

EXHIBIT 10

Opioid-free Anesthesia: Time to Regain Our Balance

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Fashions come and fashions go. Changes in clothing, automobiles, and restaurants follow popular trends and are often periodic and cyclical. Ideally, medical change is driven not by fashion but instead by concepts of effectiveness and safety, and these concepts should improve and refine as better data become available. Trends hold true also in anesthesia practice, where for example intraoperative opioid selection has swung from long-duration to ultra-short duration and then at least partially back again.¹ Recent years have witnessed a new fashion in anesthesiology: “opioid-free anesthesia.” For some, the opioid pendulum has swung clear past rational opioid use in balanced anesthesia to eliminating opioids intraoperatively and sometimes also postoperatively (opioid-free analgesia). Eradicating opioids from intraoperative and postoperative analgesic plans has been termed a “movement,”² and like many “movements,” it has attracted passionate proponents and spirited debate.^{3,4} Nevertheless, clinical research and peer-reviewed evidence on the potential benefits and risks of opioid-free anesthesia have remained scant, needed, and called for.⁵⁻⁷

This issue of *ANESTHESIOLOGY* features two articles on opioid-free anesthesia that bring some light to the heat of the debate. The original investigation by Beloeil *et al.*⁸ reports the results of a randomized clinical trial of balanced anesthesia with either remifentanyl or dexmedetomidine (opioid-free). The review by Shanthanna *et al.*⁹ provides a narrative exposition of opioid-free *versus* opioid-sparing approaches in the perioperative period. These articles are timely and important.

The clinical trial⁸ was investigator-initiated, multicenter, randomized, prospective, parallel-group, and single-blind, conducted in 10 centers in France, with an independent data and safety monitoring board to oversee the conduct and review safety data. Patients undergoing



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(adverse events) occurred in significantly more dexmedetomidine (78%) than opioid (68%) patients (relative risk, 1.16), because of a greater incidence of hypoxemia but not more ileus or cognitive dysfunction. Times to extubation and postanesthesia care unit discharge were significantly longer in the dexmedetomidine than the opioid group. Although dexmedetomidine patients had lower rates of nausea and vomiting, postoperative morphine consumption was statistically but not clinically meaningfully less (median, 3 mg difference), and postoperative pain scores, intensive care unit admission, and length of stay did not differ between groups. The authors concluded that balanced opioid-free anesthesia with dexmedetomidine increased serious adverse events and they questioned the benefit of eliminating intraoperative opioids in favor of dexmedetomidine.

This investigation is important because it evaluated both the benefits and risks of an opioid-free anesthetic regimen in a carefully controlled and blinded randomized trial. Any benefits were negligible. It is rare and concerning when a clinical trial is terminated for safety. Moreover, the adverse

major noncardiac surgery received intraoperative balanced anesthesia featuring opioids (remifentanyl infusion and morphine) or dexmedetomidine infusion (opioid-free) and postoperative morphine. The primary outcome was a composite of opioid-related adverse events (hypoxemia, ileus, or cognitive dysfunction) in the 48h postoperatively. Secondary outcomes included postoperative pain, opioid consumption, nausea and vomiting, and times to extubation and postanesthesia care unit discharge.

Frighteningly, the investigation was stopped prematurely because of safety concerns. Specifically, there were five cases of severe bradycardia in the dexmedetomidine group, including three cases of asystole. The composite primary endpoint

Image: J. P. Rathmell.

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events in this trial were not strictly related to dexmedetomidine dose, meaning that they are less predictable and that reducing the dose may not be a strategy for mitigation. This investigation exemplifies the critical need for carefully assessing the safety of multimodal regimens (and, in this case, opioid-free anesthesia), in addition to potential benefit, as has been called for previously in this journal^{10–12} and by others.^{13,14} Case in point, a four-drug intraoperative non-opioid regime added no benefit to standard anesthesia and did not appreciably change postoperative opioid use or pain scores despite the greatly increased complexity of the anesthetics.¹² The trial reported by Beloeil *et al.*⁸ clearly demonstrates that we can do more harm than good by eliminating intraoperative opioids, depending on how we replace them.

The narrative review⁹ is comprehensive and concludes that although complete opioid sparing is possible in some contexts and procedures, there is no evidence that opioid-free strategies (1) have benefits above and beyond opioid-sparing strategies, (2) influence the risk or prevent persistent postoperative opioid use, or (3) prevent postoperative opioid overprescription. In fact, there is little reason to suppose any of these hoped-for benefits would accrue. The narrative remarks that opioid-free strategies, however noble in their cause, do not fully acknowledge the limitations and gaps in existing evidence and clinical practice considerations; do not allow analgesic titration based on patient needs; are unclear about optimal nonopioid components; have ill-defined roles in different surgical settings and perioperative phases; necessitate additional equipment, monitoring, resources, and cost; ignore concerns about safety and drug interactions; do not serve to decrease the risk of persistent opioid use; and, as a result, are unrealistic in routine clinical practice. Perhaps most importantly, the undue focus on opioid-free anesthesia may be distracting us from optimizing pain relief and minimizing long-term harms.

Looking Back

What are the antecedents and potential drivers of “opioid-free anesthesia”? These may include inappropriate overreaction to the opioid crisis, opioid sparing taken to an extreme, and misinterpretation of contemporary emphasis on enhanced recovery after surgery guidelines.

The Opioid Crisis

The current opioid crisis emanated from inappropriate prescribing, marketing, diversion, and misuse of oral prescription opioids for acute and chronic noncancer pain. The human and economic toll is staggering (400,000 U.S. deaths over the past two decades, one quarter of which may be suicides, and \$2.5 trillion costs for just 2015 to 2018, including \$700 billion in 2018 alone—3.4% of the U.S. gross domestic product),^{15–18} and the problem is not limited to the United States.¹⁹ Whether *via* the medical or lay press,

no one is unaware of the opioid crisis, and opioid overdose has worsened with the COVID-19 pandemic.

The opioid crisis has multiple antecedents, and the roots are even deeper than popular narratives and current medical literature portray. Opioids have been used medicinally for millennia. However, more recent and successive waves of use have culminated in our current predicament. In the first wave (1960s), acute pain management with oral opioids was so common that propoxyphene was the second most commonly dispensed drug in the United States.²⁰ A second wave (1990s) saw further increases in oral opioid use for chronic pain treatment despite unclear evidence of effectiveness.²⁰ A third wave (2001 to 2010) saw further expanded oral opioid use, with aggressive marketing, liberalized prescribing, and proliferating managed care, regulatory agency, and practice efficiency guidelines that encouraged expanded opioid prescribing. Indeed, from 2006 to 2010, hydrocodone–acetaminophen was the most widely prescribed drug in the United States.²¹ Commensurate with increased oral opioid use during that time, the annual overdose deaths involving prescription oral opioids escalated by 182% (fig. 1).^{22,23} The fourth, most recent, and most devastating wave of opioid overdoses relates to escalating heroin and illicit fentanyl use (fig. 1), economic stress and employment deterioration,²⁴ a shift of the abused opioid supply chain from medical to illicit sources, and a fluid substitution of illicit fentanyl for prescription opioids. Overall opioid prescribing has fortunately receded,²⁵ yet overdose deaths have negligibly changed because of this more lethal wave of heroin and illicit fentanyl abuse.^{26,27}

The point is this: Notably absent from this entire historical narrative is any mention of, association with, or causal attribution of the opioid crisis to intraoperative and immediate postoperative use of opioids to treat moderate-to-severe surgical pain. Similarly, it is a great and unfounded leap to say that there is an opioid crisis and therefore we must stop using opioids for surgery. However, the steady drumbeat of the opioid crisis can influence practitioner behavior, voluntarily or subconsciously. If the concept and practice of “opioid-free” anesthesia is a response to the opioid crisis, it is unnatural, unfounded, and perplexing.

Opioid Sparing *versus* Opioid Eradication

With the shift from balanced intraoperative anesthesia and postoperative analgesia with opioids as the only analgesic component to current concepts of balanced anesthesia and multimodal analgesia with opioids and other drugs, perhaps then just dropping opioids altogether was somehow seen as a logical or natural progression. After all, we have regional anesthesia, lidocaine, ketamine, and other drugs that can contribute to the analgesic components of anesthetics. Opioids do have untoward side effects, the most bothersome being nausea and vomiting and the most dangerous being respiratory depression. Multimodal analgesic therapy is based on the theory of combining drugs to achieve additive benefit

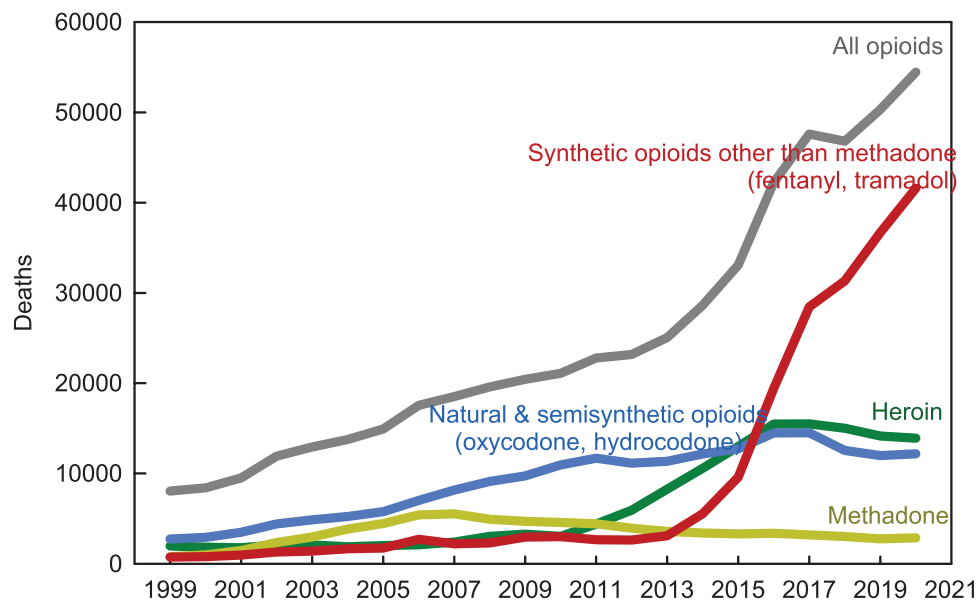


Fig. 1. U.S. drug overdose deaths involving opioids 1999 to 2020 (November), by type of opioid. The data can be accessed at <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>.

without additive risk or synergistic benefit with only additive risk. Multimodal approaches can clearly reduce pain and opioid consumption in some circumstances. All is not pure benefit, however, because many adjuvant drugs can actually increase the very side effects that are unwanted or introduce new risks. For example, gabapentinoids, sedative-hypnotics, benzodiazepines, and “muscle relaxants” (e.g., baclofen and carisoprodol) can produce additive or even potentiate opioid-induced respiratory depression.^{28–30} This is not more benefit with less risk, but in fact more risk with less benefit.

Perhaps then the thinking was to change further, to ideally eliminate untoward opioid drug interactions by just eliminating opioids altogether. The problem is that opioids are the most efficacious analgesics available in many situations, and the remaining multimodal components alone are insufficiently effective against moderate-to-severe pain. No amount of wishing will turn acetaminophen into hydro-morphone. Although opioid sparing (if it means avoiding excessive opioid use) is appropriate, opioid eradication, as identified by Shanthanna *et al.*,⁹ is not, based on evidence to date. Opioid sparing is not synonymous with opioid absence.

Enhanced Recovery after Surgery and Opioids

The objective of enhanced recovery after surgery protocols is to restore patients to their presurgical state of health as quickly as possible, as well as to reduce complications and standardize perioperative care to minimize variability and improve outcomes.¹³ Postoperative recovery is influenced primarily by minimally invasive (laparoscopic)

surgical approaches and postoperative care (e.g., oral intake, early ambulation), and only one of the five key enhanced recovery protocol components originally associated with improved outcomes relates to anesthesia (epidurals in open colectomy).^{13,14} Nevertheless, enhanced recovery protocols have been increasingly laden by well intentioned clinicians with more and more elements, simply added under the assumption they will provide additional benefit. Unfortunately, these protocols and assumptions are often untested, unvalidated, and of unknown benefit and risk.¹⁴

Also problematic is that enhanced recovery protocols and consensus statements may overstate and/or misinterpret published literature to support assertions about opioids and the value of opioid eradication, and it is important to separate evidence from conventional wisdom and assumption. For example, a consensus review of optimal perioperative care in colorectal surgery from the Enhanced Recovery After Surgery Group³¹ claimed that the adverse effects of opioids can hamper recovery and prolong length of stay, citing a Cochrane review, yet that review did not address opioids. A set of clinical practice guidelines for enhanced recovery after colon and rectal surgery from the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons claimed that multiple prospective studies (citing four) demonstrated that minimizing opioids was associated with earlier return of bowel function and shorter length of stay, yet inspection of those four studies found that none evaluated the specific contribution of postoperative opioids in isolation, and none eliminated opioid use entirely.³² Less may be better, but it

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is not clear that none is best. Such overstatements notwithstanding, enhanced recovery protocols do not universally advocate for opioid eradication over rational use. Even the most recent enhanced recovery guidelines state that opioids cannot necessarily be avoided and that analgesia is best provided by opioid sparing, not by opioid eradication.³³

Looking Forward

It is time to regain our balance in anesthesia. Opioid-free anesthesia may be *feasible*. Nevertheless, it appears neither logical nor beneficial to patients. Feasibility is not a therapeutic indication, nor is it patient-centric. In a hierarchical progression of values from feasible (can it be done?) to viable (does it have value?) to worthwhile (does it meet patient needs?) to desirable (do patients want it?) to optimal (does it best meet patient needs and optimize outcome?), feasibility is the lowest of value propositions.

Surgery hurts. Patients suffer from acute postoperative pain. More than 80% of patients report their postoperative pain is not adequately treated, a metric unchanged for decades.^{34–36} Depriving patients of analgesic opioids is unlikely to improve that metric. Additionally, poorly controlled acute postoperative pain is the greatest risk factor for chronic postoperative pain, which afflicts 10 to 60% of surgical patients.^{37,38} Moreover, acute postoperative pain is associated with complications, both generalized (postoperative cognitive decline, delirium, and sleep disturbances³⁹) and surgical (surgical site and urinary tract infections,⁴⁰ 30-day infection rates,⁴¹ and higher readmission rates⁴²). So too is chronic postsurgical pain associated with postoperative complications.⁴³ Patients who experience postoperative pain have poorer recovery, less satisfaction, and more regret about having had surgery.⁴⁴ Nonopioid approaches to treating acute postoperative pain such as local and regional anesthesia, which are hoped to prevent the transition to chronic postoperative pain, and nonopioid analgesics such as nonsteroidal anti-inflammatory drugs, *N*-methyl-D-aspartate–receptor antagonists, and gabapentinoids have, unfortunately, not been successful.³⁸ The history of excessive and inappropriate outpatient prescribing of oral opioids for chronic pain should not motivate the withholding of opioids for acute perioperative surgical pain. As stated previously, “perioperative practitioners should avoid making surgical patients pay with unnecessary suffering for the opioid overprescribing sins of others.”⁷

The clinical trial report⁸ and the comprehensive review⁹ in this issue of *ANESTHESIOLOGY* demonstrate that it is time for the opioid pendulum to swing back from the unjustified extreme of opioid eradication to a more balanced and rational approach.⁷ Although it is well known that *excessive* opioid use can have adverse consequences that can and should be mitigated, swinging completely to the *absence* of opioids, in the name of whatever well-intentioned motivation, can also have adverse consequences that can and should be mitigated. There is a Goldilocks zone for opioids in which

patients are provided the optimal balance of analgesia with minimal or no side effects or risks. The problem is that one dose regimen does not fit all. Personalized medicine is difficult to protocolize.

The challenge is to devise regimens, optimize drug selection, and deliver care that provides optimal intraoperative and immediate postoperative analgesia and ideally also confers long-lasting benefit with improved recovery trajectories.⁴⁵ For example, and the exact opposite of opioid eradication, the long-duration opioid methadone not only reduces intraoperative and immediate postoperative pain and opioid requirements but also reduces pain and opioid consumption long after patients have left the healthcare institution.^{46–49} An “opioid-sparing opioid” like methadone might confer advantage over opioid eradication.

Optimal postoperative analgesia will only be achieved by using the available tools in a manner tailored to the specific needs of individual patients. Our preoccupation with opioid-free anesthesia and analgesia distracts us from this challenge. What is clear is that our current analgesic pharmacologic armamentarium is inadequate to the task of providing adequate pain relief with minimal side effects, and it has not materially changed in decades. While academia and industry regroup after years of failures, hopefully new molecular, cellular, and systems-based approaches will help us to discover novel approaches to analgesia. In the meantime, we can work on using existing tools more effectively. We have not defined the optimal components of multimodal analgesic pathways, nor have we developed tailored approaches consistent with the goals of precision medicine. Rather than toss aside opioids, some of our most powerful tools, we should focus on defining the optimal use of these important drugs.

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Competing Interests

Dr. Clark has a consulting agreement with Teikoku Pharma USA, San Jose, California. Dr. Kharasch declares no competing interests.

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References

1. Kharasch ED: Opioid half-lives and hemlines: The long and short of fashion. *ANESTHESIOLOGY* 2015; 122:969–70

2. Society for Opioid Free Anesthesia. Available at: <https://goopioidfree.com/>. Accessed December 15, 2020.
3. Lirk P, Rathmell JP: Opioid-free anaesthesia: Con: It is too early to adopt opioid-free anaesthesia today. *Eur J Anaesthesiol* 2019; 36:250–4
4. Lavand'homme P: Opioid-free anaesthesia: Pro: Damned if you don't use opioids during surgery. *Eur J Anaesthesiol* 2019; 36:247–9
5. Wu CL, King AB, Geiger TM, Grant MC, Grocott MPW, Gupta R, Hah JM, Miller TE, Shaw AD, Gan TJ, Thacker JKM, Mythen MG, McEvoy MD; Fourth Perioperative Quality Initiative Workgroup: American Society for Enhanced Recovery and Perioperative Quality Initiative joint consensus statement on perioperative opioid minimization in opioid-naïve patients. *Anesth Analg* 2019; 129:567–77
6. Egan TD: Are opioids indispensable for general anaesthesia? *Br J Anaesth* 2019; 122:e127–35
7. Kharasch ED, Avram MJ, Clark JD: Rational perioperative opioid management in the era of the opioid crisis. *ANESTHESIOLOGY* 2020; 132:603–5
8. Beloeil H, Garot M, Lebuffe G, Gerbaud A, Bila J, Cuvillon P, Dubout E, Oger S, Nadaud J, Becret A, Coullier N, Lecoœur S, Fayon J, Godet T, Mazerolles M, Atallah F, Sigaut S, Choinier P-M, Asehnoune K, Roquilly A, Chanques G, Esvan M, Futier E, Laviolle B, POFA Study Group, SFAR Research Network: Balanced opioid-free anesthesia with dexmedetomidine *versus* balanced anesthesia with remifentanyl for major or intermediate noncardiac surgery: The POFA randomized clinical trial. *ANESTHESIOLOGY* 2021; 134:541–51
9. Shanthanna H, Ladha KS, Kehlet H, Joshi GP: Perioperative opioid administration: A critical review of opioid-free *versus* opioid-sparing approaches. *ANESTHESIOLOGY* 2021; 134:645–59
10. Kharasch ED, Eisenach JC: Wherefore gabapentinoids? Was there rush too soon to judgment? *ANESTHESIOLOGY* 2016; 124:10–2
11. Kharasch ED, Clark JD, Kheterpal S: Perioperative gabapentinoids: Deflating the bubble. *ANESTHESIOLOGY* 2020; 133:251–4
12. Maheshwari K, Avitsian R, Sessler DI, Makarova N, Tanios M, Raza S, Traul D, Rajan S, Manlapaz M, Machado S, Krishnaney A, Machado A, Rosenquist R, Kurz A: Multimodal analgesic regimen for spine surgery: A randomized placebo-controlled trial. *ANESTHESIOLOGY* 2020; 132:992–1002
13. Joshi GP, Kehlet H: Enhanced recovery pathways: Looking into the future. *Anesth Analg* 2019; 128:5–7
14. Memtsoudis SG, Poeran J, Kehlet H: Enhanced recovery after surgery in the United States: From evidence-based practice to uncertain science? *JAMA* 2019; 321:1049–50
15. Oquendo MA, Volkow ND: Suicide: A silent contributor to opioid-overdose deaths. *N Engl J Med* 2018; 378:1567–9
16. Council of Economic Advisers: The full cost of the opioid crisis: \$2.5 trillion over four years. 2019. Available at: <https://www.whitehouse.gov/articles/full-cost-opioid-crisis-2-5-trillion-four-years/>. Accessed December 15, 2020.
17. Hubbard WK: Getting serious about opioid regulation. *JAMA Intern Med* 2020; 180:309–10
18. The Economist: The wider effects of America's opioid epidemic. 2020. Available at: <https://www.economist.com/business/2020/01/16/the-wider-effects-of-americas-opioid-epidemic>. Accessed December 15, 2020.
19. Verhamme KMC, Bohnen AM: Are we facing an opioid crisis in Europe? *Lancet Public Health* 2019; 4:e483–4
20. Dasgupta N, Beletsky L, Ciccarone D: Opioid crisis: No easy fix to its social and economic determinants. *Am J Public Health* 2018; 108:182–6
21. Stoddard KI, Huggett DB: Wastewater effluent hydrocodone concentrations as an indicator of drug disposal program success. *Bull Environ Contam Toxicol* 2015; 95:139–44
22. Council of Economic Advisors: The role of opioid prices in the evolving opioid crisis. Washington, D.C., The White House, 2019
23. Hedegaard H, Miniño AM, Warner M: Drug overdose deaths in the United States, 1999–2018. Hyattsville, Maryland, National Center for Health Statistics, 2020
24. Seltzer N: The economic underpinnings of the drug epidemic. *SSM Popul Health* 2020; 12:100679
25. Zhu W, Chernew ME, Sherry TB, Maestas N: Initial opioid prescriptions among U.S. commercially insured patients, 2012–2017. *N Engl J Med* 2019; 380:1043–52
26. Alpert A, Powell D, Pacula RL: Supply-side drug policy in the presence of substitutes: Evidence from the introduction of abuse-deterrent opioids. *Am Econ J Econ Policy* 2018; 10:1–35
27. Wilson N, Kariisa M, Seth P, Smith H 4th, Davis NL: Drug and opioid-involved overdose deaths: United States, 2017–2018. *MMWR Morb Mortal Wkly Rep* 2020; 69:290–7
28. Verret M, Lauzier F, Zarychanski R, Perron C, Savard X, Pinard AM, Leblanc G, Cossi MJ, Neveu X, Turgeon AF; Canadian Perioperative Anesthesia Clinical Trials (PACT) Group: Perioperative use of gabapentinoids for the management of postoperative acute pain. *ANESTHESIOLOGY* 2020; 133:265–79
29. Izrailtyan I, Qiu J, Overdyk FJ, Ersilon M, Gan TJ: Risk factors for cardiopulmonary and respiratory arrest in medical and surgical hospital patients on opioid analgesics and sedatives. *PLoS One* 2018; 13:e0194553

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30. Li Y, Delcher C, Wei YJ, Reisfield GM, Brown JD, Tighe P, Winterstein AG: Risk of opioid overdose associated with concomitant use of opioids and skeletal muscle relaxants: A population-based cohort study. *Clin Pharmacol Ther* 2020; 108:81–9
31. Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, von Meyenfeldt MF, Fearon KC, Revhaug A, Norderval S, Ljungqvist O, Lobo DN, Dejong CH; Enhanced Recovery After Surgery (ERAS) Group: Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg* 2009; 144:961–9
32. Carmichael JC, Keller DS, Baldini G, Bordeianou L, Weiss E, Lee L, Boutros M, McClane J, Feldman LS, Steele SR: Clinical practice guidelines for enhanced recovery after colon and rectal surgery from the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons. *Dis Colon Rectum* 2017; 60:761–84
33. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, Rockall TA, Young-Fadok TM, Hill AG, Soop M, de Boer HD, Urman RD, Chang GJ, Fichera A, Kessler H, Grass F, Whang EE, Fawcett WJ, Carli F, Lobo DN, Rollins KE, Balfour A, Baldini G, Riedel B, Ljungqvist O: Guidelines for perioperative care in elective colorectal surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations: 2018. *World J Surg* 2019; 43:659–95
34. Wu CL, Berenholtz SM, Pronovost PJ, Fleisher LA: Systematic review and analysis of postdischarge symptoms after outpatient surgery. *ANESTHESIOLOGY* 2002; 96:994–1003
35. Gan TJ: Poorly controlled postoperative pain: Prevalence, consequences, and prevention. *J Pain Res* 2017; 10:2287–98
36. Meissner W, Zaslansky R: A survey of postoperative pain treatments and unmet needs. *Best Pract Res Clin Anaesthesiol* 2019; 33:269–86
37. Perkins FM, Kehlet H: Chronic pain as an outcome of surgery: A review of predictive factors. *ANESTHESIOLOGY* 2000; 93:1123–33
38. Glare P, Aubrey KR, Myles PS: Transition from acute to chronic pain after surgery. *Lancet* 2019; 393:1537–46
39. Wu CL, Rowlingson AJ, Partin AW, Kalish MA, Courpas GE, Walsh PC, Fleisher LA: Correlation of postoperative pain to quality of recovery in the immediate postoperative period. *Reg Anesth Pain Med* 2005; 30:516–22
40. van Boekel RLM, Warlé MC, Nielen RGC, Vissers KCP, van der Sande R, Bronkhorst EM, Lerou JGC, Steegers MAH: Relationship between postoperative pain and overall 30-day complications in a broad surgical population: An observational study. *Ann Surg* 2019; 269:856–65
41. Albers KI, van Helden EV, Dahan A, Martini CH, Bruintjes MHD, Scheffer GJ, Steegers MAH, Keijzer C, Warlé MC: Early postoperative pain after laparoscopic donor nephrectomy predicts 30-day postoperative infectious complications: A pooled analysis of randomized controlled trials. *Pain* 2020; 161:1565–70
42. Hernandez-Boussard T, Graham LA, Desai K, Wahl TS, Aucoin E, Richman JS, Morris MS, Itani KM, Telford GL, Hawn MT: The fifth vital sign: Postoperative pain predicts 30-day readmissions and subsequent emergency department visits. *Ann Surg* 2017; 266:516–24
43. Willingham M, Rangrass G, Curcuro C, Ben Abdallah A, Wildes TS, McKinnon S, Kronzer A, Sharma A, Helsten D, Hall B, Avidan MS, Haroutounian S: Association between postoperative complications and lingering post-surgical pain: An observational cohort study. *Br J Anaesth* 2020; 124:214–21
44. Berkowitz R, Vu J, Brummett C, Waljee J, Englesbe M, Howard R: The impact of complications and pain on patient satisfaction. *Ann Surg* 2019 Oct 28 [Epub ahead of print]
45. Kharasch ED, Brunt LM: Perioperative opioids and public health. *ANESTHESIOLOGY* 2016; 124:960–5
46. Kharasch ED: Intraoperative methadone: Rediscovery, reappraisal, and reinvigoration? *Anesth Analg* 2011; 112:13–6
47. Murphy GS, Szokol JW: Intraoperative methadone in surgical patients: A review of clinical investigations. *ANESTHESIOLOGY* 2019; 131:678–92
48. Komen H, Brunt LM, Deych E, Blood J, Kharasch ED: Intraoperative methadone in same-day ambulatory surgery: A randomized, double-blinded, dose-finding pilot study. *Anesth Analg* 2019; 128:802–10
49. Murphy GS, Avram MJ, Greenberg SB, Shear TD, Deshur MA, Dickerson D, Bilimoria S, Benson J, Maher CE, Trenk GJ, Teister KJ, Szokol JW: Postoperative pain and analgesic requirements in the first year after intraoperative methadone for complex spine and cardiac surgery. *ANESTHESIOLOGY* 2020; 132:330–42